CHAPTER 12

Esophageal cancer

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Although still relatively uncommon in Western countries, esophageal cancer is fatal in the vast majority of cases. In the United States, an estimated 14,520 new cases will be diagnosed in the year 2005, and 13,570 deaths will result from the disease. This high percentage of deaths rivals that of pancreatic cancer and is more than four times that of rectal cancer.

The esophagus extends from the cricopharyngeal sphincter to the gastroesophageal (GE) junction and is commonly divided into the cervical, upper to mid-thoracic, and thoracic portions. This can be important, as histology and optimal treatment approaches may vary considerably based on the site of the cancer. It may not be possible to determine the site of origin if the cancer involves the GE junction itself.

Epidemiology

Gender Esophageal cancer is seven times more common and slightly more lethal in men than in women.

Age Adenocarcinoma of the esophagus (now more common in the United States than the squamous cell type) has a median age at diagnosis of 69 years. The incidence of squamous cell cancer of the esophagus increases with age as well and peaks in the seventh decade of life.

Race The incidence of squamous cell esophageal cancer is three times higher in blacks than in whites, whereas adenocarcinomas are more common in white men.

Geography Evidence for an association between environment and diet and esophageal cancer comes from the profound differences in incidence observed in different parts of the world. Esophageal cancer occurs at a rate 20-30 times higher in China than in the United States. An esophageal "cancer belt" extends from northeast China to the Middle East.

Survival Although the overall outlook for patients diagnosed with esophageal cancer has improved in the past 30 years, most patients still present with advanced disease, and their survival remains poor. One-third to one-half of patients treated with either chemoradiation therapy or chemoradiation therapy plus surgery are alive at 2 years, without recurrence of esophageal cancer.

Disease site The rate of cancer of the distal esophagus is about equal to that of the more proximal two-thirds. In general, squamous cell carcinoma is found in

the body of the esophagus, whereas adenocarcinoma predominates in lesions closer to the GE junction.

Etiology and risk factors

Cigarettes and alcohol Squamous cell carcinomas of the esophagus have been associated with cigarette smoking and/or excessive alcohol intake. Furthermore, cigarette smoking and alcohol appear to act synergistically, producing high relative risks in heavy users of tobacco and alcohol. Esophageal adenocarcinoma is increased twofold in smokers.

Diet High-fat, low-protein, and low-calorie diets have been shown to increase the risk of esophageal cancer. Exposure to nitrosamines has been proposed as a factor in the development of both squamous cell carcinoma and adenocarcinoma of the esophagus.

Barrett's esophagus and other factors Gastroesophageal reflux disease (GERD) and Barrett's esophagus (adenomatous metaplasia of the distal esophagus) have been linked to adenocarcinoma of the esophagus. Tylosis, Plummer-Vinson syndrome, history of head and neck cancer, and achalasia have also been associated with a higher-than-normal risk of developing squamous cell cancer of the esophagus.

Signs and symptoms

Because symptoms do not alert the patient until the disease is advanced, few esophageal cancers are diagnosed at an early stage.

Dysphagia The most common presenting complaint is dysphagia, which generally is not noted until the esophageal lumen is narrowed to one-half to one-third of normal, due to its elasticity.

Weight loss is common and has a significant role in prognosis (> 10% of total body weight as poor prognosis).

Cough that is induced by swallowing is suggestive of local extension into the trachea with resultant tracheoesophageal fistula.

Odynophagia and pain Pain with swallowing (odynophagia) is an ominous sign. Patients who describe pain radiating to the back may well have extraesophageal spread. Supraclavicular or cervical nodal metastases may be appreciated on examination.

Hoarseness may be a sign of recurrent laryngeal nerve involvement due to extraesophageal spread.

Metastatic disease may present as malignant pleural effusion or ascites. Bone metastasis can be identified by pain involving the affected site or by associated hypercalcemia. The most common metastatic sites are retroperitoneal or celiac lymph nodes.

The American College of Surgeons conducted a study utilizing its national cancer database to assess the presentation, stage distribution, and treatment of pa-

tients diagnosed with esophageal cancer between 1994 and 1997 (n = 5,044). The most common presenting symptoms were dysphagia (74.0%), weight loss (57.3%), reflux (20.5%), odynophagia (16.6%), and dyspnea (12.1%). Fifty percent of patients had tumors located in the lower third of the esophagus. Squamous cell histology was found in 51.6%, and 42.0% of patients had adenocarcinomas. Barrett's esophagus was found in 39% of those patients with adenocarcinoma. Patients undergoing initial surgical resection had the following stage distribution: stage I (13.3%), II (34.7%), III (35.7%), and IV (12.3%).

Diagnosis

In Western countries, the diagnosis of esophageal cancer is generally made by endoscopic biopsy of the esophagus. In the Far East, cytologic evaluation is frequently utilized.

Endoscopic ultrasonography (EUS) is extremely accurate (> 90%) in establishing the depth of tumor invasion (T stage) but less accurate (70%-80%) in determining nodal involvement (N stage) unless combined with fine-needle aspiration (FNA) of the involved nodes (93% accuracy) when nodes greater than 5 mm are biopsied. The addition of FNA increases the sensitivity from 63% to 93% and the specificity from 81% to 100%. EUS is not reliable in determining the extent of response to neoadjuvant treatment.

Endoscopy and barium x-rays Endoscopy allows for direct visualization of abnormalities and directed biopsies. Barium x-rays are less invasive and provide a good assessment of the extent of esophageal disease.

Bronchoscopy should be performed to detect tracheal invasion in all cases of esophageal cancer except adenocarcinoma of the distal third of the esophagus.

CT scan Once a diagnosis has been established and careful physical examination and routine blood tests have been performed, a CT scan of the chest, abdomen, and pelvis should be obtained to help assess tumor extent, nodal involvement, and metastatic disease.

PET A prospective trial designed to evaluate the utility of PET vs CT and EUS was performed by obtaining these studies in 48 consecutive patients prior to esophagectomy. PET achieved a 57% sensitivity, 97% specificity, and 86% accuracy compared with CT, which was 99% sensitive, 18% specific, and 78% accurate. In terms of nodal staging, PET was correct in 83% of cases, as compared with 60% of cases for CT and 58% for EUS ($P = .006$). This analysis suggests the improved accuracy of PET in the staging work-up of patients with esophageal cancer.

Numerous studies report the accuracy of PET scanning in determining the presence of metastatic disease, with sensitivity approaching 90% and specificity over 90%.

As PET becomes more widely available, its use will probably become an important part of the preoperative evaluation of these patients. In a prospective trial of 39 patients with esophageal cancer, PET detected additional sites of metastatic disease at the initial evaluation when compared with conventional

A prospective follow-up study of 161 patients with Barrett's esophagus who underwent serial endoscopy was presented at the 2004 ASCO meeting. Two patients developed adenocarcinoma, with a mean follow-up of 4.3 years. Patients with longer lengths of Barrett's esophagus (mean 7.6 cm) were more likely to develop cancer than those with shorter lengths (mean 4.6 cm); *Ahn S-H, Garewal HS, Sampliner RE, et al: Proc Am Soc Clin Oncol [abstract] 23:314, 2004*).

imaging. After induction therapy, PET did not add to the estimation of locoregional resectability and did not detect new distant metastases. However, this study suggested that changes in [^{18}fluorodeoxyglucose] FDG-PET following induction therapy may predict disease-free and overall survival after induction therapy and resection in patients with esophageal cancer. A large prospective national trial will evaluate the use of PET scan in the treatment of esophageal cancer.

Bone scan A bone scan should be obtained if the patient has bone pain or an elevated alkaline phosphatase level.

Thoracoscopy/laparoscopy Investigators have recently begun to examine the role of surgical staging prior to definitive therapy. These procedures are designed to allow pathologic review of regional lymph nodes and the accurate assessment of extraesophageal tumor spread by direct visualization. A recently completed multi-institution trial (Cancer and Leukemia Group B [CALGB] 9380) found these procedures to be feasible in over 70% of patients; they resulted in the upstaging of patients in 38% of cases reviewed. Further investigations need to be completed to determine the appropriate use of these tools in treatment algorithms for patients with esophageal cancer.

Warning Staging studies should be undertaken only if management would change on the basis of specific findings.

Screening and surveillance

HIGH-RISK PATIENTS

Adenocarcinoma The role of screening patients with GERD and surveillance of patients with Barrett's esophagus by upper GI endoscopy remains under investigation. In 833 patients studied by endoscopy, there was a 13% incidence of intestinal metaplasia (Barrett's esophagus). Dysplasia or cancer was seen in 31% of patients with long-segment Barrett's esophagus, in 10% of short-segment Barrett's esophagus, and in 6% of GE-junction intestinal metaplasia.

Squamous cell carcinoma Mass screening in the high-risk areas of China and Japan is considered appropriate.

Pathology

Adenocarcinoma The incidence of esophageal adenocarcinoma involving the GE junction has risen 4%-10% per year since 1976 in the United States and Europe. As a result, adenocarcinoma is now the predominant histologic subtype of esophageal cancer. The distal one-third of the esophagus is the site of origin of most adenocarcinomas.

TABLE 1: 1983 and 2002 AJCC TNM staging systems for esophageal cancer

1983 Classification (clinical)				2002 Classification (pathologic)		
Primary tumor (T)						
Tis	Carcinoma in situ			Same		
T1	Tumor involves ≤ 5 cm of esophageal length, produces no obstruction, and has no circumferential involvement			Tumor invades lamina propria or submucosa		
T2	Tumor involves > 5 cm of esophageal length, causes obstruction, or involves the circumference of the esophagus			Tumor invades muscularis propria		
T3	Extraesophageal spread			Tumor invades adventitia		
T4	Not applicable			Tumor invades adjacent structures		
Regional lymph nodes (N)						
Nx	Regional nodes cannot be assessed			Same		
N0	No nodal metastases			No regional nodal metastases		
N1	Unilateral, mobile, regional nodal metastases (if clinically evaluable)			Regional nodal metastases		
N2	Bilateral, mobile, regional nodal metastases (if clinically evaluable)			Not applicable		
N3	Fixed nodes			Not applicable		
Distant metastases (M)						
M0	No distant metastases			Same		
M1	Distant metastases			Distant metastases		
				Tumors of lower thoracic esophagus: M1a Metastases in celiac lymph nodes M1b Other distant metastases		
				Tumors of mid-thoracic esophagus: M1a Not applicable M1b Nonregional lymph nodes and/or other distant metastases		
				Tumors of upper thoracic esophagus: M1a Metastases in cervical nodes M1b Other distant metastases		
Stage grouping						
Stage I	T1	N0 or NX	M0	T1	N0	M0
Stage II	T2	N0 or NX	M0			
Stage IIA				T2-3	N0	M0
Stage IIB				T1-2	N1	M0
Stage III	T3	Any N	M0	T3 T4	N1 Any N	M0 M0
Stage IV	Any T	Any N	M1	Any T	Any N	M1
Stage IVA				Any T	Any N	M1a
Stage IVB				Any T	Any N	M1b

TABLE 2: Treatment options and survival by stage in esophageal cancer

Stage[a]	Standard treatment	5-Year survival rate (%)
Stage 0 (Tis N0 M0)	Surgery	> 90
Stage I (T1 N0 M0)	Surgery	> 70
Stage IIA (T2-3 N0 M0)	Surgery, chemoradiation therapy, or combination	15-30
Stage IIB (T1-2 N1 M0)	Surgery, chemoradiation therapy, or combination	10-30
Stage III (T3 N1 M0 or T4 Any N M0)	Chemoradiation therapy Palliative resection of T3a tumors	< 10
Stage IV (Any T Any N M1)	Radiation therapy ± intraluminal intubation and dilation ± chemotherapy	Rare

[a] According to the AJCC TNM system definitions (see Table 1)

Note: Surgical results are based on the pathologic staging system, whereas patients treated with combined-modality therapy or neoadjuvant chemoradiation therapy are clinically staged.

Squamous cell carcinomas occur most often in the proximal two-thirds of the esophagus. Squamous cell carcinoma is still the most prevalent histologic subtype worldwide.

Other tumor types Other, less frequently seen histologic subtypes include mucoepidermoid carcinoma, small-cell carcinoma, sarcoma, adenoid cystic leiomyosarcoma, and primary lymphoma of the esophagus. Occasionally, metastatic disease from another site may present as a mass in the esophagus or a mass pressing on the esophagus.

Metastatic spread The most common sites of metastatic disease are the regional lymph nodes, lungs, liver, bone, adrenal glands, and diaphragm. Adenocarcinoma can also metastasize to the brain.

Staging and prognosis

Based on data demonstrating that the depth of penetration has important prognostic significance, the American Joint Committee on Cancer (AJCC) TNM staging system for esophageal cancer was changed from a clinical one (1983) to a pathologic one in 2002. Both the clinical and pathologic staging systems are shown in Table 1, as patients may be cured without an operation. Although pathologic information obtained from an esophagectomy specimen is of prognostic importance, postoperative therapy to improve prognosis has not been rigorously tested. Moreover, recurrence rates for stage I (30%) and stage II (70%) cancers suggest early systemic spread undetected by current noninvasive staging.

TABLE 3: Chemotherapy regimens for esophageal carcinoma

Drug/combination	Dose and schedule
Cisplatin/fluorouracil/radiation therapy	
Cisplatin	75 mg/m^2 IV on day 1 of weeks 1, 5, 8, and 11
Fluorouracil	1 g/m^2/d IV infused continuously on days 1-4 of weeks 1, 5, 8, and 11
Radiation therapy	200 cGy/d 5 days per week (total regional treatment, 3,000 cGy), followed by a 2,000-cGy boost field (total, 5,000 cGy) in 5 weeks
Give chemotherapy concurrently with radiation therapy.	

Adapted from Herskovic A, Martz K, al-Sarraf M, et al: N Engl J Med 326:1593–1598, 1992.

Table prepared by Ishmael Jaiyesimi, DO

Pathologic information obtained from an esophagectomy specimen is of significant prognostic importance. Immunohistochemical analysis of the initial biopsy specimen may also have prognostic relevance. Clinical staging has been shown to be of prognostic importance, particularly in patients managed with primary radiotherapy or chemoradiation therapy.

Histology and grade Neither histology nor grade has been shown to be of prognostic importance in esophageal carcinoma.

Other prognostic factors Patient age, performance status, and degree of weight loss are of prognostic importance. The prognostic implications of tumor-suppressor genes and oncogenes are an area of active investigation.

Treatment

Treatment options for the various disease stages are given in Table 2, along with 5-year survival rates.

TREATMENT OF LOCALIZED DISEASE

Only 40%-60% of patients with esophageal cancer present with clinically localized disease. National Comprehensive Cancer Network (NCCN) guidelines state that patients with clinically localized disease may be treated with resection or chemotherapy plus irradiation (Tables 3 and 4). The overall 5-year survival rates for either surgery alone or combined chemotherapy and irradiation appear equivalent.

Chemoradiation therapy as primary management of localized or locoregionally confined esophageal cancer has been shown to be superior to irradiation alone. A series of randomized trials have demonstrated that adjuvant postoperative chemoradiation therapy does not offer a survival advantage to patients with esophageal cancer. Adequate patient selection, tumor staging, and treat-

TABLE 4: Chemotherapy regimens for gastric esophageal cancer

Dose/combination	Dose and schedule
Adjuvant fluorouracil/leucovorin/radiation therapy for gastric and gastroesophageal junction adenocarcinoma	
Fluorouracil	425 mg/m^2 IV on days 1-5
Leucovorin	20 mg/m^2 IV on days 1-5 immediately before fluorouracil for one cycle then 3-4 weeks later
Followed by	
Radiation therapy	4,500 cGy (180 cGy a day) given concurrently with
Fluorouracil	400 mg/m^2 IV on days 1-4 and on the last 3 days of radiation therapy
Leucovorin	20 mg/m^2 IV on days 1-4 and on the last 3 days of radiation therapy
One month after completion of radiation therapy:	
Fluorouracil	425 mg/m^2 IV on days 1-5
Leucovorin	20 mg/m^2 IV on days 1-5 immediately before fluorouracil
Repeat cycle every 28 days for 2 cycles.	

Adapted from Macdonald JS, Smalley S, Benedetti J, et al: Proc Am Soc Clin Oncol 19:1, 2000.

Table prepared by Ishmael Jaiyesimi, DO

ment standardization will be required before the optimal therapeutic modalities in these patients will be determined.

Surgery

Preoperative medical evaluation helps determine the patient's risk of developing postoperative complications and mortality. In addition to the staging and nutritional status, it should include an evaluation of the pulmonary, cardiac, renal, and hepatic functions.

Extent of surgical resection The extent of resection depends on the location of the primary tumor, histology of the tumor, and nature of the procedure (palliative vs curative). Retrospective study has reported that superficial mucosal lesions may be treated via endoscopic mucosal resection, but those patients with submucosal invasion require esophagectomy. For tumors of the intrathoracic esophagus (squamous cell carcinomas) and tumors with extensive Barrett's esophagus (adenocarcinomas), it is necessary to perform a total esophagectomy with cervical anastomosis to achieve a complete resection. For distal lesions of the abdominal esophagus (adenocarcinomas) and cardia, it is often possible to perform an intrathoracic esophageal anastomosis above the azygus vein, although many surgeons would prefer to perform a total esophagectomy.

The resected esophagus may be replaced with tubularized stomach in patients with tumors of the intrathoracic esophagus or with a colon interposition in patients with tumors involving the proximal stomach, since such involvement makes this organ unsuitable for esophageal reconstruction. The esophageal replacement is usually brought up through the posterior mediastinum, although the retrosternal route is often used in palliative procedures.

Patient selection The indications for esophagectomy in esophageal cancer vary from center to center within the United States.

Clearly, patients with distant metastases, evidence of nodal metastases in more than one nodal basin, or tumor extension outside the esophagus (airway, mediastinum, vocal cord paralysis) are candidates for palliative therapy. Patients with disease limited to the esophagus and no evidence of nodal metastases (stages I and IIA) may be treated with esophagectomy, although these patients can also be considered for definitive treatment with chemoradiation therapy.

Sentinel node biopsy has proved to be accurate in establishing lymph node staging in patients with melanoma, breast cancer, and, most recently, colorectal cancer. The authors studied this technique in 25 patients who had technetium-99m colloidal rhenium sulfide injected submucosally the day before surgery. Lymphoscintigraphy detected sentinel lymph nodes in 92% of patients. The accuracy of sentinel lymph node biopsy was 91.3%, the sensitivity was 86.7%, and the false-negative rate was 8.7% without cytokeratin staining. When cytokeratin staining was added, occult metastasis was detected in 14 of the 25 patients (56%) and in 23 of the 1,406 lymph nodes (1.7%), and the accuracy improved to 100% (*Kato H, Miyazaki T, Nakajima M, et al: Cancer 98:932-939, 2003*).

Method of resection Considerable controversy also exists among surgeons regarding the method of resection. To date, two randomized studies have compared transhiatal esophagectomy (without thoracotomy) with the Ivor-Lewis (transthoracic) esophagectomy (with thoracotomy). These studies failed to show differences between the two procedures with regard to operative morbidity and mortality. In a recent randomized trial of 220 patients treated either with a transthoracic or transhiatal esophageal resection, there was a trend toward an improvement in 5-year survival. A meta-analysis failed to show differences in 5-year survival rates. Over the past 5 years, successful attempts have been made to use minimally invasive approaches to esophageal cancer with thoracoscopy and laparoscopy. Although those studies have shown a decrease in morbidity and the minimally invasive approach appears to be oncologically sound from the point of view of resection margins, the number of nodes resected is still not comparable to that of the standard transthoracic approach.

The need for pyloric drainage (pyloroplasty) following esophagectomy is another area of debate. A meta-analysis of nine randomized trials that included 553 patients showed a trend favoring pyloric drainage in improving gastric emptying and nutritional status, whereas bile reflux was better in the nondrainage group. The gastric emptying time evaluated by scintigraphy was twice as long in the nondrainage group than in the pyloric drainage groups.

Lymphadenectomy Considerable controversy exists regarding the need for radical lymphadenectomy in esophageal disease. Much of the controversy is due to the fact that different diseases are being compared.

Japanese series include mostly patients with squamous cell carcinomas of the intrathoracic esophagus, with 80% of the tumors located in the proximal and middle sections of the esophagus. Americans report combined series, with at least 40%-50% of patients with adenocarcinomas of the distal esophagus. Skinner and DeMeester favor en bloc esophagectomy with radical (mediastinal and abdominal) lymphadenectomy, based on 5-year survival rates of 40%-50% in patients with stage II disease, as compared with rates of 14%-22% in historic controls.

In a retrospective study, Akiyama found a 28% incidence of cervical node metastases in patients with squamous cell carcinomas located in the middle and distal portions of the esophagus, as opposed to 46% in those with tumors of the proximal third. Overall survival at 5 years was significantly better in patients who underwent extended lymphadenectomy (three fields) than in those who had conventional lymphadenectomy (two fields); this finding was true in patients with negative nodes (84% and 55%, respectively) and in those with positive nodes (43% and 28%, respectively). Extended lymphadenectomy afforded no survival advantage in patients with tumors in the distal third of the esophagus.

In a study of 1,000 patients with esophagogastric junction adenocarcinomas, the tumors were classified according to the location of the center of the tumor mass in adenocarcinomas of the distal esophagus, cardia, and subcardia. The tumors located in the cardia and subcardia regions spread primarily to the paragastric and left gastric vessel nodes and did not benefit from extended esophagectomy.

Preoperative chemotherapy

The frequency of metastatic disease as the cause of death in patients with esophageal cancer has resulted in exploration of the early application of systemic therapy in the treatment of esophageal cancer. The first of the two large studies was intergroup study 113. A total of 440 patients were treated with surgical resection alone or preceded by three cycles of cisplatin and 5-FU. Objective responses were reported in only 19% of patients receiving chemotherapy. No difference in resectability, operative mortality, median survival (14.9 months with chemotherapy vs 16.1 months with surgery alone), or 2-year survival (35% vs 37%) was reported.

However, the Medical Research Council evaluated 802 patients with resectable esophageal cancer in a similar study. Patients randomized to receive chemotherapy were administered two cycles of cisplatin (80 mg/m^2) and 5-FU (1 g/m^2/d as a continuous infusion for 4 days). Microscopically complete resection was performed more frequently in patients receiving chemotherapy, with no difference found in postoperative complications or mortality. Moreover, patients receiving neoadjuvant chemotherapy had significantly longer median

survivals (16.8 months vs 13.3 months) and 2-year survivals (43% vs 34%) than patients treated with surgery alone. The reasons for the differences in the outcomes are unclear but may be related to the chemotherapy regimen and schedule employed in the intergroup study, patient population, or study design. As a result, the role of neoadjuvant chemotherapy remains in question but is promising, especially with the potentially more efficacious newer generation of chemotherapy agents.

Polee et al have evaluated a biweekly combination of cisplatin and paclitaxel in this setting in a phase II study, with promising results. Objective responses occurred in 59% of 49 patients. No patients had progressive disease. Although 71% of patients had severe neutropenia, it was often asymptomatic. Forty-seven patients underwent resection subsequently. Complete pathologic responses occurred in 14% of patients. The median survival of patients in this study was 20 months, but it was 32 months in patients who had disease responsive to chemotherapy. The 3-year survival rate was 32%.

Given the uncertainty about the efficacy of preoperative chemotherapy and chemoradiation therapy, some investigators have administered preoperative chemotherapy, followed by chemoradiation therapy, then surgery. The true utility of this approach will need to be defined by randomized studies, but clearly, the approach is feasible, without a significant increase in toxicity or operative morbidity. Interestingly, these reports have also demonstrated that most patients had significant improvement or resolution of dysphagia with the induction chemotherapy alone.

Radiotherapy

Although radiotherapy alone is inferior to chemoradiation therapy in the management of locoregionally confined esophageal cancer, it may offer palliation to patients with advanced local disease too frail for chemotherapy.

Preoperative radiotherapy has been shown to be of little value in converting unresectable cancers into resectable ones or in improving survival. However, it decreases the incidence of locoregional recurrence.

Postoperative radiotherapy (usually to 50 or 60 Gy) can decrease locoregional failure following curative resection but has no effect on survival.

Brachytherapy Intraluminal isotope radiotherapy (intracavitary brachytherapy) allows high doses of radiation to be delivered to a small volume of tissue. Retrospective studies suggest that a brachytherapy boost may result in improved rates of local control and survival over external-beam radiotherapy

The most recent Patterns of Care Study examined patients treated between 1996 and 1999. This study revealed a statistically significant increase in the use of endoscopic ultrasonography in the pretreatment work-up of patients as compared with the original survey. There was also a significant rise in the use of concurrent chemoradiation therapy prior to planned surgical resection as compared with the original survey (27% vs 10%, *P* = .0007). Use of paclitaxel as part of the chemoradiation therapy strategy also significantly increased during this period *(.2% vs 22%, P = .0001; Suntharalingam M, Moughan J, Coia LR, et al: Int J Radiat Oncol Biol Phys 57[2 suppl]:S218, 2003).*

A German trial randomized patients to receive induction chemotherapy with 5-FU/leucovorin-etoposide/platinum followed by chemoradiation therapy to 40 Gy followed by esophagectomy, vs the same induction chemotherapy followed by chemoradiation therapy to 60 Gy (no resection). Treatment mortality was initially higher (10.2%) in those patients undergoing resection than in those not undergoing resection (3.5%), but it decreased as the trial progressed (4.2%). Local recurrence was lower in those who underwent resection (64% vs 81%; *P* = .08) and 3-year survival was higher (28% vs 20%; *P* = .022; *Stahl M, Wilke H, Walz MK, et al: Proc Am Soc Clin Oncol [abstract] 22:250, 2003).*

alone. This technique can be associated with a high rate of morbidity if not used carefully.

A multi-institution prospective trial was conducted by the RTOG to determine the feasibility and toxicity of chemotherapy, external-beam irradiation, and esophageal brachytherapy in potentially curable patients with esophageal cancer. Nearly 70% of patients were able to complete external-beam irradiation, brachytherapy, and at least two cycles of 5-FU/cisplatin. The median survival was 11 months, and the 1-year survival was 49%. Because of the 12% incidence of fistula formation, the investigators urged caution in the routine application of brachytherapy as part of a definitive treatment plan.

Chemoradiation therapy

Preoperative chemoradiation therapy Initial trials of preoperative chemoradiation therapy reported unacceptably high operative mortality (~26%). Subsequent trials reported operative mortality of 4%-11%, median survival as long as 29 months, and 5-year survival rates as high as 34%. In general, 25%-30% of patients have no residual tumor in the resected specimen, and this group tends to have a higher survival rate than those who have a residual tumor discovered by the pathologist.

The superiority of preoperative chemoradiation therapy over surgery alone in esophageal adenocarcinoma has been demonstrated in a prospective trial. This trial included 113 patients with adenocarcinoma of the esophagus. These patients were randomized to receive either preoperative chemoradiation therapy (two courses of fluorouracil [5-FU] and cisplatin given concurrently with 40 Gy of radiotherapy in 15 fractions) or surgery alone. Median survival was statistically superior in the combined-modality arm than in the surgery-alone arm (16 vs 11 months). Rates of 3-year survival again statistically favored the combined-modality arm (32% vs 6%). Although toxicity was not severe, the short survival in the surgery control arm has minimized the impact of these results in the United States.

A meta-analysis of 11 randomized trials involving 2,311 patients treated with neoadjuvant chemotherapy or chemoradiation therapy was reported. Preoperative chemotherapy improved 2-year survival compared with surgery alone: The absolute difference was 4.4% (95% confidence interval [CI], 0.3-8.5). For combined chemoradiotherapy, the increase was 6.4% (nonsignificant; 95% CI, –1.2-14.0). Treatment-related mortality increased by 1.7% with neoadjuvant chemotherapy (95% CI, –0.9-4.3) and by 3.4% with chemoradiotherapy (95% CI, –0.1-7.3) compared with surgery alone (*Kaklamanos IG, Walker GR, Ferry K, et al: Ann Surg Oncol 10:754-761, 2003*).

A trial performed at the University of Michigan enrolled 100 patients and randomized

them to undergo surgery alone or preoperative chemoradiation therapy (cisplatin, 20 mg/m^2/d), 5-FU (300 mg^2/d), and vinblastine (1 mg/m^2/d) and radiotherapy (45 Gy/1.5 Gy bid). With a median follow-up of 8.2 years, the 3-year survival was 16% (surgery alone) vs 30% (induction chemoradiation therapy). This difference did not reach statistical significance, as the study was designed to detect a relatively large increase in median survival from 1 to 2.2 years. A meta-analysis of randomized trials comparing neoadjuvant chemoradiation therapy followed by surgery with surgery alone found that neoadjuvant concurrent chemoradiation therapy improved 3-year survival (odds ratio, 0.66) compared with surgery alone, with a nonsignificant trend toward increased mortality with neoadjuvant treatment.

Newer chemotherapy agents are active and may improve outcome over these older trials. A phase II trial of 129 patients employed paclitaxel/carboplatin [Paraplatin]/5-FU with 45 Gy of radiation therapy followed by esophagectomy. A pathologic complete response was seen in 38% of patients, with a median survival of 22 months and a 3-year survival of 41%.

Another phase II trial from the University of Michigan administered paclitaxel/cisplatin with 45 Gy of radiation therapy twice daily (1.5 Gy bid). In this study, 19% of patients exhibited a pathologic complete response, with a 24-month median survival and a 3-year survival of 34%. Ongoing studies by the Radiation Therapy Oncology Group (RTOG) are employing these newer chemotherapy agents.

Primary chemoradiation therapy Patients with locally advanced esophageal cancer (T1-4 N0-1 M0) may be cured with definitive chemoradiation therapy. Randomized trials have demonstrated a survival advantage for chemoradiation therapy over radiotherapy alone in the treatment of esophageal cancer. In an RTOG randomized trial involving 129 patients with esophageal cancer, irradiation (50 Gy) with concurrent cisplatin and 5-FU provided a significant survival advantage (27% vs 0% at 5 years) and improved local control over radiation therapy alone (64 Gy). Median survival also was significantly better in the combined-therapy arm than in the irradiation arm (14.1 vs 9.3 months).

A recently completed randomized intergroup trial was designed to investigate the role of high-dose irradiation in conjunction with systemic therapy. This study compared doses of 50.4 Gy with 64.8 Gy. Both treatment arms of the study administered concurrent 5-FU and cisplatin. This trial was stopped after an interim analysis revealed no statistically significant difference in survival between the two groups. The authors concluded that higher dose radiation therapy did not offer any survival benefit compared with the 50.4-Gy dose.

Patient selection Patients with disease involving the mid to proximal esophagus are excellent candidates for definitive chemoradiation therapy because resection in this area can be associated with greater morbidity than resection of more distal tumors.

Most of the trials demonstrating the efficacy of chemoradiation therapy have had a high proportion of patients with squamous cell cancers. Chemoradiation therapy has thus become a standard treatment of locoregionally confined squa-

mous cell cancer of the esophagus. It is essential that chemotherapy be given concurrently with irradiation when this approach is chosen as primary treatment for esophageal cancer. A typical regimen is 50-60 Gy over 5-6 weeks, with cisplatin (75 mg/m^2) and 5-FU (1 g/m^2/24 h for 4 days) on weeks 1, 5, 8, and 11.

The literature also supports offering patients with adenocarcinoma primary surgery, preoperative chemoradiation therapy, or primary chemoradiation therapy with surgical salvage if necessary. Entering these patients on protocols will allow us to further define standard treatment.

Sequential preoperative chemotherapy and radiation therapy Only modest benefits have been found with preoperative chemoradiation therapy to date, with systemic failure continuing to be an important problem. Thus, sequential therapy with chemotherapy followed by chemoradiation therapy has been explored.

Ajani et al reported a series of 43 patients who received 12 weeks of cisplatin and irinotecan (Camptosar) followed by weekly paclitaxel with infusional 5-FU and concurrent radiation therapy (4,500 cGy) and then esophagectomy. Therapy was well tolerated, with no deaths from chemotherapy or chemoradiation therapy, and an operative mortality rate of 5%. Cisplatin and irinotecan induced responses in 37% of patients, and 91% of patients underwent complete resection. Pathologic complete responses occurred in 26% of patients, and some tumor shrinkage was noted in 63% of patients. With a median follow-up of more than 30 months, the median disease progression-free survival was 10. 2 months, the median survival was 22.1 months, and the 2-year survival was 42%. The patients who had a pathologic response to therapy had significantly better outcomes than the rest of the study population. However, systemic recurrences remained a prominent cause of failure, with five patients experiencing recurrence first in the brain and an additional five patients, in the liver.

Esophagectomy following chemoradiation therapy Considerable controversy exists regarding the need for esophagectomy following chemoradiation therapy. The incidence of residual disease in patients who have a complete clinical response to chemoradiation therapy is 40%-50%. Patients with complete response following chemoradiation therapy have the best survival rates with surgery.

TREATMENT OF ADVANCED DISEASE

The goal of esophageal cancer treatment is generally palliative for patients with bulky or extensive retroperitoneal lymph nodes or distant metastatic disease. Therapeutic approaches should temper treatment-related morbidity with the overall dismal outlook.

Local treatment In patients with a good performance status, the combination of 5-FU/mitomycin (Mutamycin), or 5-FU/cisplatin, and radiotherapy (50 Gy) results in a median survival of 7-9 months. This regimen usually renders patients free of dysphagia until death.

Photodynamic therapy (PDT) Porfimer sodium (Photofrin) and an argon-pumped dye laser can provide effective palliation of dysphagia in patients with esophageal cancer. A prospective, randomized multicenter trial comparing PDT with neodymium/yttrium-aluminum-garnet (Nd:YAG) laser therapy in 236 patients with advanced esophageal cancer found that improvement of dysphagia was equivalent with the two treatments.

A recent review of 119 patients treated with endoluminal palliation reported a significant improvement in dysphagia scores and an increased ability to relieve stenosis caused by tumor when PDT was used in conjunction with laser therapy and irradiation.

Other approaches include external-beam radiotherapy with or without intracavitary brachytherapy boost, simple dilatation, placement of stents, and laser recannulization of the esophageal lumen.

Palliative resection for esophageal cancer is rarely warranted, although it does provide relief from dysphagia in some patients.

Chemotherapy Recently published phase I and II studies have demonstrated moderate response rates to taxanes in esophageal cancer. Taxanes in combination with platinum compounds and fluoropyrimidines are being tested in regimens with irradiation.

Although chemotherapy alone may produce an occasional long-term remission, there is no standard regimen for patients with metastatic cancer. Patients with advanced disease should be encouraged to participate in well-designed trials exploring novel agents and chemotherapy combinations.

CHEMOTHERAPY IN ADVANCED ESOPHAGEAL CANCER

Advances have been made in the treatment of lower GI malignancies with new chemotherapeutic agents, particularly irinotecan and oxaliplatin (Eloxatin). Progress has been slower, however, for treatment of upper GI malignancies. Given the different etiologies of the predominant forms of esophageal cancer, one problem in assessing the efficacy of chemotherapy in this disease is the fact that it remains uncertain whether squamous cell carcinomas and adenocarcinomas respond differently to chemotherapy. To date, both histologies appear to respond similarly to chemotherapy.

Limited data from randomized studies are available regarding the use of chemotherapy in metastatic esophageal cancer. Most current data come from phase II studies, making treatment recommendations difficult. In light of the limited efficacy of current chemotherapeutic agents and available data about the newer agents, no standard therapy for advanced esophageal carcinoma presently exists.

The mainstay of therapy for advanced esophageal cancer has been cisplatin, which produces responses in approximately 15%-35% of patients, with a median survival of about 4-6 months. With the addition of 5-FU as a 5-day continuous infusion (in a manner similar to its use in squamous cell carcinoma of the head and neck), a modest increase in response rates to approximately 25%-35% occurs, but with no clear improvement in survival rates.

In Britain, the ECF regimen, a combination of epirubicin (Ellence, 50 mg/m^2) and cisplatin (60 mg/m^2), both repeated every 21 days, with continuous infusion of 5-FU (200 mg/m^2/d), is considered to be a standard regimen for advanced esophagogastric cancers. Several phase III studies have been performed and consistently demonstrated objective responses in about 40% of patients, with a median survival of 9 months and 1-year survival of 36%-40%. The main severe toxicities of this regimen are neutropenia, in about one-third of patients (32%-36%), lethargy (18%), and nausea and vomiting (11%-17%).

Attempts to improve the efficacy of this regimen, which is logistically difficult to administer, are ongoing. Given the accepted role of capecitabine (Xeloda), a 5-FU prodrug, in colorectal and breast cancers, as well as oxaliplatin, a study evaluating the potential roles of these drugs is being performed. Sumpter et al have reported the preliminary data from their study, with results suggesting similar efficacy and toxicity with the different combinations. The final results will not be available for several years but are eagerly awaited. A regimen with intravenous chemotherapy on one day combined with oral capecitabine, rather than infusional 5-FU, would gain much greater acceptance than ECF if the efficacy and toxicity of the regimens are similar.

With the advent of many new chemotherapeutic agents (the taxoids, paclitaxel and docetaxel [Taxotere], irinotecan, and gemcitabine [Gemzar]) with varying mechanisms of activity, further studies have been conducted, and each of these drugs has demonstrated activity, with responses achieved in approximately 15%-30% of patients (Table 5).

However, the primary route of investigation for these new agents has been in combination with cisplatin and/or 5-FU. The results available to date suggest promising activity, with response rates often around 50% in phase II studies. Irinotecan (65 mg/m^2) and cisplatin (30 mg/m^2) administered weekly for 4 weeks every 6 weeks have also been active, with responses in 20 of 35 patients (57%) and an impressive median survival of 14.6 months.

Following the example of the combination of irinotecan and 5-FU/leucovorin in colon cancer, the investigators have explored a modification of that schedule, with therapy administered for 2 weeks, with cycles repeated every 3 weeks. This simple modification has been investigated in 27 patients and was well tolerated, with severe neutropenia in 18% of patients and severe diarrhea in 11% of patients.

Paclitaxel (180 mg/m^2 over 3 hours) and cisplatin (60 mg/m^2 over 3 hours) administered every 14 days have been extensively evaluated in Europe and were reported to produce objective responses in 43% of 51 patients, including two complete responses, and 43% of patients were alive 1 year after initiation of therapy (Table 6).

Because of the toxic and logistic difficulties of using cisplatin, carboplatin has become a popular chemotherapeutic drug. Several studies of carboplatin with paclitaxel have been undertaken in esophageal cancer. El-Rayes et al administered carboplatin (area under the curve of 5) with paclitaxel (200 mg/m^2 over 3 hours) every 3 weeks in 33 chemotherapy-naive patients. Objective

TABLE 5: Single-agent chemotherapy

Agent	Response rate (%)
Cisplatin	6-35
Carboplatin	0-7
Fluorouracil	15-18
Paclitaxel	15-32
Docetaxel	20-30
Irinotecan	15
Vinorelbine	20
Etoposide	0-20
Gefitinib	8-12

responses were reported in 45% of patients, with a median survival of 9 months and 1-year and 2-year survival of 43% and 17%.

Polee et al explored a weekly schedule of these drugs in a phase I study. With therapy administered for 3 consecutive weeks, followed by a 1-week break, a dose of carboplatin (area under the curve of 4) with paclitaxel (100 mg/m^2) was recommended for further investigation. Responses were noted in half of the 40 patients, with a median survival of 11 months and 1-year survival of 46%. Both of these combinations were well tolerated, with the primary toxicity of myelosuppression.

The antimetabolite gemcitabine has also been evaluated in combination with cisplatin in esophageal cancer. A Southwest Oncology Group Study reported by Urba combined 1,000 mg/m^2 of gemcitabine on days 1, 8, and 15 with 100 mg/m^2 of cisplatin on day 15 in 64 patients. Approximately one-quarter of these patients had received prior chemotherapy. Therapy was well tolerated, with severe neutropenia occurring in 31% of patients. The median survival of patients treated on this study was 7.3 months, and the 1-year survival was 20%. However, the heterogeneity of the patient population makes the efficacy of the therapy somewhat difficult to assess.

Kroep et al tested a somewhat different schedule of these drugs, based on preclinical data suggesting that cytotoxicity is higher when cisplatin is administered 24 hours before gemcitabine. Thus, cisplatin (50 mg/m^2) was given on days 1 and 8, and gemcitabine (800 mg/m^2 over 30 minutes), on days 2, 9, and 16, with cycles repeated every 28 days. Objective responses were noted in 39% of 36 patients, with stable disease in 17 patients, and a median survival of 9.8 months. Aside from myelosuppression, this combination was also well tolerated.

Oxaliplatin may also have a role in the treatment of esophageal cancer, both as a radiosensitizer and an agent in advanced disease. A preliminary report dem-

TABLE 6: Combination chemotherapy

Agents	Response rate (%)	Survival
Cisplatin/fluorouracil	19-40	Median = 7 months, 1 year = 27%
Cisplatin/paclitaxel	37-43	Median = 6-9 months
Cisplatin/gemcitabine	38-47	Median = 7-10 months
Cisplatin/irinotecan	57	Median = 14.6 months
Cisplatin/vinorelbine	33	Median = 6.8 months
Cisplatin/etoposide	45-48	Median = 8-10 months, 1 year = 26%-41%
Epirubicin/cisplatin/ fluorouracil	40-42	Median = 9 months, 1 year = 36%-40%
Cisplatin/fluorouracil/ paclitaxel	48	Median = 10.8 months, 1 year = 38%
Carboplatin/paclitaxel	45-50	Median = 9-11 months, 1 year = 43%-46%

onstrated objective responses in 48% of 29 evaluable patients treated with oxaliplatin, 5-FU, and leucovorin according to the FOLFOX 4 schedule (oxaliplatin, 85 mg/m^2 on day 1; leucovorin, 500 mg/m^2 over 2 hours on days 1 and 2; and 5-FU, 400 mg/m^2 bolus, then 600 mg/m^2 over 22 hours on days 1 and 2, repeated every 14 days).

The primary toxicity of these regimens is severe neutropenia, occurring in about 40%-70% of patients. Severe diarrhea, nausea, and vomiting occur in ~10%-15% of patients in many studies. Fatigue and asthenia also were significant side effects with both therapies.

With improving toxicity profiles and modest improvements in therapeutic outcomes, second-line therapy for advanced esophageal cancer is also increasingly being explored. Muro et al treated 28 Japanese patients with squamous cell carcinoma of the esophagus with docetaxel (70 mg/m^2) every 3 weeks; these patients had previously received cisplatin and 5-FU. As expected, severe neutropenia was the dominant toxicity (88%, including nine episodes of febrile neutropenia), with severe anorexia, fatigue, and anemia also reported. Objective responses were noted in 16% of these patients.

In addition, Lordick et al determined that irinotecan (55 mg/m^2) and docetaxel (25 mg/m^2) given on days 1, 8, and 15, with cycles repeated every 28 days, were tolerable, with severe asthenia in 21% of 24 patients and severe diarrhea in 13%. However, only three partial responses (13%) and eight patients with stable disease were noted, with a resultant median survival of 26 weeks. Although these studies suggest the feasibility of second-line cytotoxic chemo-

therapy in esophageal cancer, the significant toxicity and limited objective response rate warrant its use only with caution and preferably on a clinical study.

Novel agents are also being actively investigated, with great hope for the future. The combination of paclitaxel with the cyclin-dependent kinase inhibitor flavopiridol has demonstrated promising activity in patients with esophageal cancer. A phase I study of this combination reported one complete, one partial, and one minor response in seven patients treated.

In addition to flavopiridol and the epidermal growth factor receptor antagonists, it is anticipated that other targeted therapies, such as vascular endothelial growth factor antagonists, will be evaluated in this disease. Such avenues of exploration, in addition to early diagnosis and therapy for early-stage disease, are the most likely path toward significant improvements in the therapy of esophageal cancer.

Oral tyrosine kinase inhibitors of the epidermal growth factor receptor have also been investigated in esophageal cancer. Gefitinib (Iressa), at a daily dose of 500 mg, was evaluated as second-line therapy in esophageal adenocarcinomas, with partial responses in 12% of 26 patients, with an additional 12 patients having stable disease (*Ferry DR, Anderson M, Beddows K, et al: Proc Am Soc Clin Oncol [abstract] 23:317, 2004*). A similar patient population was studied, with similar results: partial responses in 3 of 34 patients (8%) and stable disease in 6 patients. Toxicities were expected, rash, diarrhea, vomiting, and transaminase level elevation (*Van Groeningen C, Richel D, Giaccone G, et al: Proc Am Soc Clin Oncol [abstract] 23:318, 2004*). However, another study found only 1 response in 23 patients treated with erlotinib (150 mg daily; *Radovich D, Kelsen D, Shah M, et al: Proc Am Soc Clin Oncol [abstract] 23:331, 2004*). As with lung cancer, the optimal population for therapy with these targeted therapies remains to be elucidated.

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